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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NEGIN, RUSSELL SCOTT	
ART UNIT	**PAPER NUMBER**
1631	

DATE MAILED: 06/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/832,786	DILLER ET AL.	
	Examiner	Art Unit	
	Russell S. Negin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 11-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 11-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

DETAILED ACTION

CLAIM REJECTIONS - 35 USC § 112

The rejections of claims 16-17 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement are withdrawn due to arguments made by the applicant in the Remarks of March 27, 2006 on pages 1-2.

CLAIM REJECTIONS - 35 USC § 103

The rejection of claims 1-3, 5, 11-13, and 15 under 35 U.S.C. 103(a) as being unpatentable over Ho et al. (1994) in view of Rarey et al. (J. Mol. Biol., 1996) is withdrawn due to amendments made to the set of claims submitted on March 27, 2006.

The rejection of claims 4 and 14 under 35 U.S.C. 103(a) as being unpatentable over Ho et al. (1 994) in view of Rarey et al (J. Mol. Biol., 1996), as applied to claims 1-3, 5, 11-13, and 15 above, further in view of Aldenderfer et al. (1984) is withdrawn due to amendments made to the set of claims submitted on March 27, 2006.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4, 5, 11, 12, and 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rarey et al [Journal of Computer-Aided Molecular Design, volume 10, 1996, pages 41-54] in view of Ho et al [Proceedings of the Twenty-Seventh Annual Hawaii International Conference on System Sciences, 1994, Volume V, pages 213-222].

Claims 1 and 11 are a method, program storage device for assessing a combinatorial library for complementarity to a target of known three-dimensional structure, having at least one binding site, said combinatorial library comprising a plurality of ligands, each based on a common core, said method comprising docking each ligand of said plurality of ligands to the target molecule in a plurality of ligand-target molecule complex formations, said plurality of ligand positions comprising a plurality of common core positions relative to the target molecule; determining the rms deviation of one or more common core positions of said plurality of common core positions from one or more other common core positions of said plurality of common core positions; forming clusters of ligands from said plurality of ligands according to said rms deviation; and rating complementarity of the combinatorial library to the target

molecule based at least in part on the relative number of ligands in the library that are in the largest cluster.

Claims 2 and 12 limit claims 1 and 11 wherein rating the complementarity of the combinatorial library to the target molecule is based on the number of ligands in a cluster having a minimum rms deviation relative to the number of ligands in the combinatorial library.

Claims 4 and 14 limit claims 1 and 11 wherein said forming clusters comprises forming clusters using a single linkage clustering algorithm.

Claim 16 is a method for assessing a combinatorial library for complementarity to a target of known three-dimensional structure, having at least one binding site, said combinatorial library comprising a plurality of ligands, each based on a common core, said method comprising docking each ligand of said plurality of ligands to the target molecule in a plurality of ligand-target molecule complex formations, said plurality of ligand positions comprising a plurality of common core positions relative to the target molecule; forming clusters of ligands from said plurality of ligands based on said plurality of common core positions relative to the target molecule; counting the number of ligands in at least one cluster; and rating complementarity of the combinatorial library to the target molecule based at least in part on the count.

Claim 17 limits claim 16 wherein the rating is based at least in part on a count of ligands in the largest of said clusters relative to the number of ligands in the library.

In the article of Rarey et al, entitled, "Placement of medium-sized molecular fragments into active sites of proteins," Rarey et al explains in the abstract, "We present

an algorithm for placing molecular fragments into the active site of a receptor." Table 2 on page 47 lists the targets with known three-dimensional structures and at least one binding site. Table 3 on page 47 lists a library of ligands.

Columns 1a and 1b in Table 5 on page 49 of Rarey et al. give the free energy estimation computed and the rms deviation of the highest ranking placement produced.

Clustering processes are explained in the second column of page 46 and page 47, which states under clustering transformations, "With the data structure developed in the previous section, we are now able to find all triangles of the interaction points in the receptor that can be mapped on a given triple of interaction centers on the ligand. Each such assignment of two triangles defines a unique transformation of the ligand into the active site such that the rms deviation between the two triples of the end points in minimal." Rarey et al. continues in the last paragraph in column 2 of page 46 by stating, "In general, complete-linkage hierarchical clustering works as follows. At the beginning, each object represents a singleton cluster. The distance between two clusters is defined as the maximum distance between the objects of the clusters. As long as the minimum distance between the two clusters is less that a given threshold τ, the following procedure is repeated: determine the two clusters with minimum distance and merge them into a single cluster. Thus, the order in which clusters are merged is determined by the distance between the clusters." Thus, the number of members of a cluster determines, in part the number of conformations that are compatible with each other and the largest cluster has the most members below a certain threshold (a threshold is a means of ranking clusters). Rarey et al states in the last paragraph of

column 1 on page 47, “A small rms deviation between the transformations of two placements means that the interactions of the two placements can take place simultaneously.”

Table 5 on page 49 of Rarey et al lists the nine ligands binding to the target, and in conformations with negative free energies and thus simultaneity in binding (a hot spot). The number of possible solutions (acceptable means of binding or energy minima) is listed in the second column of Table 5. Thus, there is a count of 18 possible conformers to ligand 1 which could be placed in clusters if the rms deviation is below a certain threshold. Such an analysis can be replicated for are nine ligands. Table 5 also rates the comformer with the most favorable binding. The number of “counts” or solutions plays a role in the likelihood that the conformer with the free energy of binding is the global minimum.

Rarey et al. implement their studies using the computer program FLEXX.

However, Rarey et al. fails to use libraries of ligand with a common core or a computer storage device.

Ho et al. describes that the various compound databases have inherent strengths and weaknesses (assessing) with regard to particular chemical classes (clustering). Further, an initial database of fragments is necessary, ligand diversity is assured through the combinatorial assortment of building blocks (page 214, left column, lines 11-15, and lines 33-37), as in instant claim 1, lines 1-4. Ho et al. describes the “common core" as defined in the instant specification, page 5, paragraph 21.

Ho et al. state that "fragments must be screened and edited to ensure steric and electrostatic complementarity. . . To accomplish this, all structures would have to be considered in regard to all bond loci in space as well as the structures and pharmacophoric elements associated with them" (page 214, left column, lines 43-46). By setting this constant distance to the radius of a molecular atom type, steric contacts are revealed where penetration of the receptor molecular surface by the ligand vector model occurs (see page 214, right column, last line, to page 215, left column, line 4). In the generation of fragments for the chain_dbase database the structures were docked in the active site with the appropriate orientation (page 216, left column, last paragraph), as in instant claim 1, lines 5-8. The use of computers and databases is described in column 2 page 215, to column 1 on page 216.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice Rarey et al. in view of Ho et al. to result in the instantly claimed invention because while both Rarey et al. and Ho et al. screen libraries of ligands for complementarity to targets using hierarchies of classes, Ho et al. has the advantage of examining combinatorial libraries of molecules with common core positions.

Claims 1, 3, 11, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rarey et al (1996a) and Ho et al. as applied to claims 1, 2, 4, 5, 11, 12, and 14-17 above, and further in view of Rarey et al. [Journal of Molecular Biology, 1996b, volume 261, pages 470-489].

Claims 1 and 11 are a method, program storage device for assessing a combinatorial library for complementarity to a target of known three-dimensional structure, having at least one binding site, said combinatorial library comprising a plurality of ligands, each based on a common core, said method comprising docking each ligand of said plurality of ligands to the target molecule in a plurality of ligand-target molecule complex formations, said plurality of ligand positions comprising a plurality of common core positions relative to the target molecule; determining the rms deviation of one or more common core positions of said plurality of common core positions from one or more other common core positions of said plurality of common core positions; forming clusters of ligands from said plurality of ligands according to said rms deviation; and rating complementarity of the combinatorial library to the target molecule based at least in part on the relative number of ligands in the library that are in the largest cluster.

Claims 3 and 13 determine the rms deviation comprising: placing a grid around the binding site of the target molecule; for each grid position, determining a location on the grid corresponding to the center of mass of the common core; and determining the rms deviation of each common core position from every other common core position having a location on the grid within a predetermined distance.

The above rejection of Rarey et al (1996a) in view of Ho et al. for claims 1, 2, 4, 5, 11, 12, and 14-17 applied above fails to describe uses of grids to obtain rms deviations.

Rarey et al. (1996b) describes a method for screening larger sets of ligands for their binding affinity to a given receptor (page 472, left column, lines 21-23). The ligand is divided into fragments. The base placement algorithm finds positions of the base fragment in the active site (page 474, left column, lines 18-31). The second step in the base placement algorithm is to cluster the placements according to an appropriate distance function such as rms deviation between two placements (page 475, left column, lines 33-37). Rarey et al. (1996b) uses a hierarchical clustering algorithm as applied to rms deviations (page 477, right column). A binding mode closely approaching the experimental geometry is predicted among the few highest-ranking placements (page 472, left column, lines 23-26), as in instant claim 1, lines 9-15, and claim 2.

Rarey et al. (1996b) further, describe the use of a cubic grid covering three-dimensional space aligned to the Cartesian coordinate axis. The grid is for checking a ligand atom for overlap with the receptor by inspecting the receptor atoms whose centers (center of mass) are located in all cubes intersecting a sphere centered in the ligand atom (page 476, left column, line 57, to right column, line 10). The distance between placements is the rms deviation between the coordinates of the ligand (rms threshold 0.7A) (page 477, right column, lines 39-45), as in instant claim 3.

Rarey et al. (1996b) describes via the images in Figures 8 and 9, for each protein-ligand interaction, a pair of matching points (hot spots) is generated resulted from searching for new interactions (page 476, right column, Searching for new interactions section). Further, Rarey et al. describes the docking procedure comprising FLEXX analyzing the structure of the ligand and detects local topological symmetries at

single bonds whose torsion angle can be changed. The computation of rms deviations also considers this local symmetry (page 478, left column, The ligand section), and the receptor has defined coordinates and crystalline position (fixed) (478, left column, The receptor section), as in instant claim 5.

Rarey et al (1996b) implements the FLEXX docking tool on a SUN SPARC station 20 (page 486, left column, Summary of results), as in instant claims 6-8, 10-13, and 15.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice Rarey et al (1996a) and Ho et al. as applied to claims 1, 2, 4, 5, 11, 12, and 14-17 above, and further in view of Rarey et al. (1996b) because Rarey et al (1996b) has the further advantage of being applicable to the use of grids for determining rms deviations.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Andrew Wang, Supervisory Patent Examiner, can be reached at (571) 272-0811.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

-RSN 6/16/2006

16 June 2006

16 June 2006
JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER